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(54) Title: PROCESS FOR PRODUCING WET RIBAVIRIN PELLETS

(57) Abstract: A process for producing wet ribavirin pellets is provided in order to make pharmaceutical dosages of ribavirin. The process is particularly useful as an alternative method for preparing pharmaceutical dosages of ribavirinthat reduces the amount ofribavirindust that is produced during the manufacturing process and allows for greater control of dissolution rates. According to the preferred embodiments, this method is accomplished through mixing ribavirinwith at least one excipient into a uniform mixture, formingthe mixture into a granulated mass by adding a wetting agent, shaping said granulated mass into soluble particles and drying the flowable particles. The process enables Ribavirinpharmaceutical p ellets to be mixed with a binder and disintegrant to form a uniform mixture.

PROCESS FOR PRODUCING WET RIBAVIRIN PELLETS

BACKGROUND OF THE INVENTION

1. Field Of The Invention

The present invention relates to a process for making oral pharmaceutical dosages of ribavirin. More specifically, the drug ribavirin is a synthetic nucleoside analog with broad spectrum antiviral activity. Ribavirin is one of a combination of drugs being administered to patients with Hepatitis C and other viral infections.

Ribavirin is currently manufactured, among other methods, using a process commonly called dry compaction. Dry compaction utilizes high pressure to form a ribbon of ribavirin that is subsequently reduced to a free flowing powder by milling. The undesirable side effects of manufacturing ribavirin by dry compaction include the creation of excessive dust, a potential health hazard, as well as the risk that high pressure, which can produce high heat, could produce polymorphic forms. Different polymorphs or combinations of polymorphs are undesirable because they can sometimes change the manner in which the active drug moiety is absorbed.

The present invention describes a method for manufacturing ribavirin using a wet granulation process. This process forms a free flowing ribavirin by mixing ribavirin with a wetting agent and various excipients to form a granulation that can be extruded and spheronized, producing a pellet. This process is not only an alternative method for producing ribavirin, but also offers several advantages over the dry compaction process. One advantage of wet granulation is that significantly less dust is produced, which is important from a health and safety standpoint. Another advantage of the present invention is that wet granulation allows for greater control of dissolution rates. In addition, this wet granulation method results in the

ribavirin having better flow characteristics, enabling faster encapsulation and lower weight variations. Finally, because there is little heat or excessive pressure, the wet granulation method lowers the risk of creating polymorphs and, therefore, allows for greater uniformity of the crystalline structure.

2. Description Of The Prior Art

It is well known in the art that a raw drug often is unsuitable for medicinal purposes because the raw drug has undesirable dissolution profiles and cannot be efficiently encapsulated because of poor flow qualities. For efficient encapsulation, proper flow is vital to producing a uniform, quality pharmaceutical product for a variety of reasons, including that these factors can affect how much active drug is absorbed and when it is absorbed into the human body.

Excipients are often added to raw drugs in order to create a mixture having improved flow, compaction, or disintegration characteristics. These excipients can add various qualities either to the end product or to some stage of the manufacturing process. Common excipients include disintegrants, lubricants, fillers, binders and wetting agents. Disintegrants absorb water quickly when the dosage form reaches the alimentary canal. Lubricants help with mold release and flow. Fillers provide bulk and, along with binders and wetting agents, add adhesion to the mixture. However, some formulas produce a finished dosage form that is too large or results in disintegration rates which could be slower or faster than is optimal.

The following three methods are commonly used to mix excipients with raw drugs to produce pharmaceutical capsules: (1) direct blend, (2) dry compaction, and (3) wet granulation. In the direct blend process, drugs and selected excipients are added to a blender and mixed in the dry state to produce a uniform distribution of the active drug. This direct blend method requires an active drug with acceptable flow characteristics. In the dry compaction process, drugs and selected excipients are mixed and then compacted into a ribbon and milled to a uniform particle size. This operation often generates heat. The result is a free flowing powder

that can be encapsulated. Finally, in the wet granulation process, the drugs are mixed either in their liquid form or with a wetting agent to produce a wet mass that can be further processed to produce a free flowing material, which in turn can be encapsulated.

Heretofore, there have been no references in the prior art that demonstrate the successful use of the wet granulation process to manufacture ribavirin capsules. Rather ribavirin is presently made using a dry compaction process as shown in Patent Nos. 6,051,252, 5,196,594 and 5,914,128. Each of Patent Nos. 6,051,252, 5,196,594 and 5,914,128 describes a method of producing dosages of ribavirin using high pressures which could generate high temperatures. Specifically, Patent Nos. 6,051,252 and 5,914,128 both describe the use of compressing forces that range from 50 to 75 kilonewtons of force.

Although the most common pharmaceutical dosage of ribavirin is 200mg, other dosages could be manufactured.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide an alternative method for preparing pharmaceutical dosages of ribavirin which reduces the amount of ribavirin dust that is produced during the manufacturing process, allows for greater control of dissolution rates, and increases flow rates. This goal is accomplished through a wet granulation process that combines ribavirin with specific disintegrants, binders, fillers, and wetting agents in sufficient quantities to form an extrudable mass.

One preferred embodiment of the invention teaches that the extrudable mass is mixed to form a uniform mixture of active drug and excipients, which mixture is subsequently formed into pellets by extrusion and spheronization.

More specifically, the present invention is a process for producing ribavirin pellets, comprising the steps of mixing ribavirin with at least one excipient into a uniform mixture; forming said uniform mixture into a granulated mass by adding a wetting agent to said uniform

mixture; shaping said granulated mass into flowable particles; and drying said flowable particles, resulting in dried flowable particles.

These objects, as well as other objects and advantages of the present invention, will become apparent from the following description, in reference to the illustrations and charts appended hereto.

BRIEF DESCRIPTION OF THE DRAWINGS

For a better understanding of the invention, refer to the accompanying chart in which Figure 1 is an electronic photograph of pellets produced by the preferred embodiment enlarged at a ratio of 1:1000.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention discloses a process for making pharmaceutical dosages of ribavirin through wet granulation. There are several formulas that can be utilized to produce ribavirin pellets by wet granulation, preferably with extrusion and spheronization.

Table 1

Formulation Ingredient	% Range of Total Formulation	Function in the Formulation
ribavirin	31 – 35	Active Pharmaceutical Ingredient
microcrystalline cellulose	27 – 35.5	Binder / Diluent
croscarmellose sodium	0 – 3	Disintegrant
polyethylene glycol	11 - 39	Binder / Wetting Agent

Under one of the preferred embodiments, the dry ingredients listed in Table 1 above are mixed together and granulated with the wetting agent, extruded through a screen (0.4 millimeter ("mm") to 1.0mm), spheronized, and fluid bed dried. Depending on the dosage required, the resulting pellets are filled into hard gelatin capsules sizes "1" to "00".

Table 2

Formulation Ingredient	% Range of Total Formulation	Function in the Formulation
ribavirin, U.S. Pharmaceutical Grade ("USP")	41 – 67	Active Pharmaceutical Ingredient
microcrystalline cellulose	24 – 33	Binder / Diluent
croscarmellose sodium	2 – 6	Disintegrant
polyethylene glycol	5 - 17	Binder / Wetting Agent
povidone	1 – 4.5	Binder
water USP	15 – 30 (calculated on a wet basis)	Wetting Agent

Under another preferred embodiment, the dry ingredients listed in Table 2 above are mixed together and granulated with the wetting agent, extruded through a screen (0.4mm to 1.0mm), spheronized, and fluid bed dried. Depending on the dosage required, the resulting pellets are filled into hard gelatin capsules sizes "1" to "00".

Table 3		
Formulation Ingredient	% Range of Total Formulation	Function in the Formulation
ribavirin USP	41 – 67	Active Pharmaceutical Ingredient
microcrystalline cellulose	24 – 33	Binder / Diluent
croscarmellose sodium	2 – 6	Disintegrant
povidone	1 – 4.5	Binder
lactose	5 – 10	Diluent
water USP	15 – 79 (calculated on a wet basis)	Wetting Agent

Under another preferred embodiment, the dry ingredients listed in the Table 3 above are mixed together and granulated with the wetting agent, extruded through a screen (0.4 mm – 1.0 mm), spheronized, and fluid bed dried. Depending on the dosage required, the resulting pellets are filled into hard gelatin capsules sizes "1" to "00".

One of the preferred embodiments results in a product that is encapsulated in size "1" or "1el" (elongated) capsules to form a 200 milligram ("mg") dose of active ribavirin. The total capsule weight is approximately 270 mg. One of the preferred embodiments also calls for a 200 mg pharmaceutical dosage in which at least 90% of the ribavirin dissolves within 30 minutes. Thus, although the method described in the claims can be used to produce ribavirin in different sized capsules or having different dissolution rates, this disclosure will only provide the detailed

weights and other measurements that will result in a capsule containing 200 mg of active ribavirin having the previously mentioned rate of dissolution.

In the aforesaid preferred embodiment, the following formulation and material quantities are used most preferably:

Table 4

Ingredient	% of Formulation	mg / Capsule	kilogram ("kg")/ 10,000 Capsules 200mg (size 1el)	kg / 10,000 Capsules 300mg (size 0)	kg / 1,000,000 Capsules 200mg (size 1el)	kg / 1,000,000 Capsules 400mg (size 00)
ribavirin USP	74	200	2	3	200	400
microcrystalline cellulose	15.6	42	0.42	0.63	42	84
croscarmellose sodium	3.7	10	0.1	0.15	10	20
povidone	1.1	3	0.03	0.045	3	6
lactose	5.6	15	0.15	0.23	15	30
water USP			1.75	2.63	165	330
Total	100	270	2.7	4.05	270	540
Total with Water USP			4.45	6.68	435	870
% Water USP in the wet granulation			39	39	38	38

Ribavirin USP is mixed for 3 to 15 minutes along with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and povidone K 27-33 in a suitably sized granulator. Purified water USP is added to the mixture at a rate of 2 kg to 50 kg per minute. The wet mass is granulated for an additional 30 seconds to 20 minutes (depending on batch size).

After granulating, the wet mass is fed into an extruder at a rate that avoids product stagnation and excessive accumulation. The extruded mass is spheronized on an appropriately sized marumerizer or equivalent equipment using typical parameters. Typical parameters used during said spheronization include those listed as follows:

Jacket water temperature	45-60°C
Groove plate configuration	Medium
Marumerizer speed setting	0.5-1.0
Spherionization time	0.5-2 minute/portion

In the aforesaid preferred embodiment, the pellets are fluid-bed dried.

Drying is continued until the pellets having a loss on drying (LOD) of not more than 5% and not less than 0.5% is achieved. Following drying, the pellets are sieved by use of a 16 mesh or 18 mesh screen.

After the pellets are sieved, said pellets can be used to fill a capsule employing standard encapsulators. In this preferred embodiment, the capsule is a size 1 elongated capsule which will have a desired total capsule fill weight of 270 mg.

Said preferred embodiment produces a dosage in which at least 90% will dissolve in 30 minutes. However, it is anticipated within this application that future uses of ribavirin may lead to a demand for ribavirin dosages having a different dissolution profile. Therefore, this invention discloses and claims the addition of coatings to the dried pellets to yield other dissolution profiles. Coatings in common use include polymethacrylic, dyethyl-aminophyl, polyethanene glycols and other excipients well known in the art.

CLAIMS

We Claim:

1. A process for producing ribavirin pellets, comprising the steps of:

mixing ribavirin with at least one excipient into a uniform mixture;

forming said uniform mixture into a granulated mass by adding a wetting agent to said uniform mixture;

shaping said granulated mass into flowable particles; and drying said flowable particles.

2. A process according to Claim 1, wherein said excipient is povidone, starch, lactose, polyethylene glycol, and hydroxy propylmethyl cellulose.

3. A process according to Claim 1, wherein said excipient is selected from a group consisting of croscarmellose sodium, starch, cellulose, bentonite, and cross-povidones.

4. A process according to Claim 1, wherein said wetting agent consists of purified water USP.

5. A process according to Claim 1, wherein a filler is added to the ribavirin.

6. A process according to Claim 5, wherein said filler is selected from a group consisting of microcrystalline cellulose, lactose, sucrose, cellulose and starch.

7. A process according to Claim 5, wherein said step of mixing is accomplished by adding said filler in accordance with said uniform mixture, resulting in said uniform mixture consisting of ingredients containing between 40% and 50% filler by weight.

8. A process according to Claim 1, wherein said step of mixing is accomplished by adding excipient, resulting in said uniform mixture consisting of ingredients containing from 1% to 9% excipient by weight.

9. A process according to Claim 1, wherein said step of mixing is accomplished by adding said ribavirin, resulting in said uniform mixture consisting of ingredients

containing between 35% to 80% ribavirin by weight.

10. A process according to Claim 1, wherein achievement of a granulated mass is accomplished by said step of mixing until a smooth granulated mass is formed.

11. A process according to Claim 1, wherein said step of shaping is accomplished by a further step of spheronizing said granulated mass until uniform sized pellets are produced.

12. A process according to Claim 11, wherein said step of shaping is accomplished by said step of spheronizing said granulated mass until said uniform sized pellets are produced and by a further step of extruding said uniform sized pellets through a screen whereby said screen ranges in size from a 0.40 mm screen to a 1.0 mm screen.

13. A process according to Claim 1, wherein said step of drying is accomplished through a further step of heating said mixture to a temperature ranging from 35° Celsius to 45° Celsius, until said mixture contains a moisture content ranging from 0.5% to 5.0%.

14. A process according to Claim 1, wherein a capsule is filled with said dried flowable particles.

15. A process for producing ribavirin pharmaceutical pellets, comprising the steps of:

mixing said ribavirin USP with a filler, a disintegrant and a lubricant resulting in a mixture containing a range from 40% to 50% of said filler by weight, a range from 1% to 9% of said disintegrant by weight and a range from 35% to 80% of said ribavirin by weight;

adding sufficient wetting agent to said mixture, resulting in the formation of an extrudable mass;

shaping said extrudable mass into pellets; and

drying said pellets.

16. A process according to Claim 15, wherein said filler is selected from the group consisting of microcrystalline cellulose, lactose, sucrose, cellulose and starch.

17. A process according to Claim 15, wherein said disintegrant is a selected from a group consisting of croscarmellose sodium, starch, cellulose and bentonite.

18. A process according to Claim 15, wherein said step of shaping is accomplished by a further step of spheronizing said extruded mass until a uniform size of said pellets is produced.

19. A process according to Claim 15, wherein said step of shaping is accomplished by a further step of spheronizing said extrudable mass until a uniform size of pellets is produced and a further step of extruding said pellets through a screen, whereby said screen ranges in size from a .40 mm screen to a 1.0 mm screen.

20. A process according to Claim 15, wherein said step of drying is accomplished by a further step of heating said mixture to a temperature ranging from 35° Celsius to 45° Celsius until said mixture produces a moisture content ranging from 0.5% and 5.0%.

21. A process according to Claim 15, wherein a size "1" capsule is completely filled with said dried pellets such that the filled capsule is produced containing a range of 180 mg to 220 mg of said ribavirin, resulting in said size 1 capsule and having a total weight ranging from 243 mg to 297 mg.

22. A process according to Claim 15, wherein a size "1el" capsule is completely filled with said dried pellets such that the filled capsule is produced containing a range of 180 mg to 220 mg of said ribavirin, resulting in said size 1el capsule and having a total weight ranging from 243 mg to 297 mg.

23. A process according to Claim 15, wherein a size "0" capsule is completely filled with said dried pellets such that the filled capsule is produced containing a range of 270 mg to 330 mg of said ribavirin, resulting in said size 0 capsule and having a total

weight ranging from 364 mg to 446 mg.

24. A process according to Claim 15, wherein a size "00" capsule is completely filled with said dried pellets such that the filled capsule is produced containing a range of 360 mg to 440 mg of said ribavirin, resulting in said size 00 capsule and having a total weight ranging from 486 mg to 594 mg.

25. A process for producing ribavirin pharmaceutical pellets comprising the steps of:

mixing said ribavirin pharmaceutical pellets with microcrystalline cellulose, resulting in said ribavirin and said microcrystalline cellulose forming a mixture containing a range of from 40% to 50% of said microcyrstalline cellulose by weight and a range of from 35% to 80% of said ribavirin by weight;

adding sufficient croscarmellose sodium to said mixture such that the mixed ingredients contain a range from 1% to 9% croscarmellose sodium by weight;

forming said mixed ingredients into an extrudable mass by adding water;

shaping said extrudable mass into pellets;

drying said pellets to produce dried pellets; and

filling capsules with said dried pellets.

26. A process according to Claim 25, wherein said step of shaping is accomplished by a further step of spherionizing said extrudable mass, resulting in a production of uniform sized pellets.

27. A process of Claim 26, wherein said step of shaping is accomplished by a further step of extruding said pellets through a screen ranging from a 0.40 mm screen to a 1.0 mm screen.

28. A process according to Claim 25, wherein said screen is sized between 0.4 mm and 1.0 mm.

29. A process according to Claim 25, wherein said step of drying is accomplished through heating of said mixed ingredients to a temperature ranging from 35° Celsius

to 45° Celsius until said mixed ingredients contain a moisture content ranging from 0.5% to 5.0 %.

30. A process according to Claim 25, wherein a size "1" of said capsules is completely filled, resulting in said pellets containing a total weight ranging from 243 mg to 297 mg.

31. A process according to Claim 25, wherein a size "1el" of said capsules is completely filled, resulting in said pellets containing a total weight ranging from 243 mg to 297 mg.

32. A process according to Claim 25, wherein a size "0" of said capsules is completely filled, resulting in said pellets containing a total weight ranging from 364 mg to 446 mg.

33. A process according to Claim 25, wherein a size "00" of said capsules is completely filled, resulting in said pellets containing a total weight ranging from 486 mg to 594 mg.

34. A process according to Claim 1, wherein at least 90% of said ribavirin dissolves in 30 minutes.

35. A process according to Claim 15, wherein at least 90% of said ribavirin dissolves in 30 minutes.

36. A process according to Claim 1, wherein a coating is added to said dried pellets on an outside surface before encapsulation, resulting in a decreased rate of release during a given time span in comparison to said release under a condition without said coating.

37. A process according to Claim 15, wherein a coating is added to said dried pellets on an outside surface before encapsulation, resulting in a decreased rate of release during a given time span in comparison to said release under a condition without said coating.

38. A process according to Claim 25, wherein a coating is added to said dried pellets on an outside surface before encapsulation, resulting in a decreased rate of release during a given time span in comparison to said release under a condition without said coating.

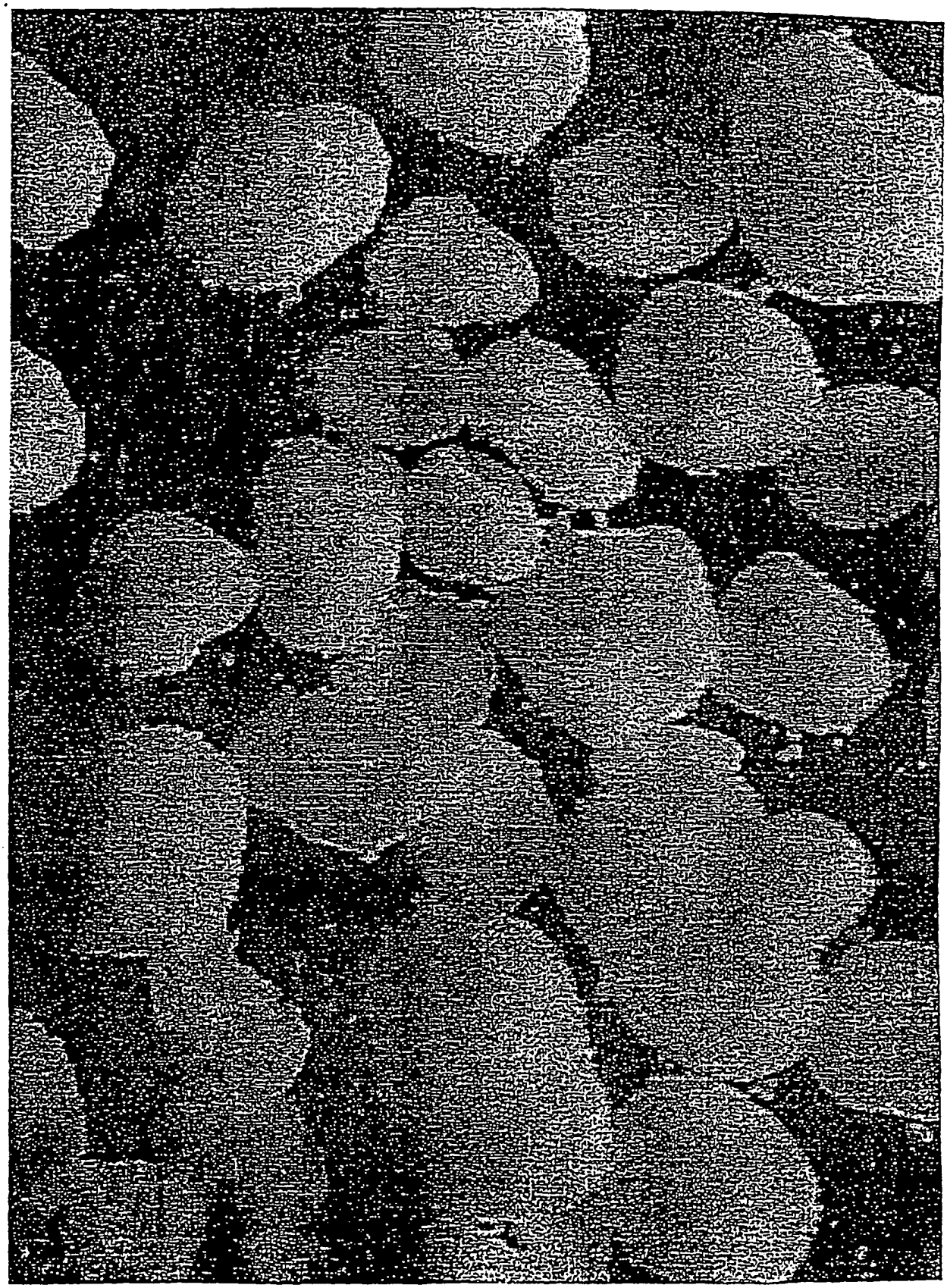

Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/08032

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/70; 9/48
US CL :514/43; 424/451

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/43; 424/451

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,798,209 A (WITKOWSKI et al.) 19 March 1974, see entire document.	1-38
Y	US 3,948,885 A (WITKOWSKI et al.) 06 April 1976, see entire document.	1-38
Y	US 3,976,545 A (WITKOWSKI et al.) 24 August 1976, see entire document.	1-38
Y	US 4,138,547 A (CHRISTENSENet al.) 06 February 1979, see entire document.	1-38
Y	US 5,767,097 A (TAM) 16 June 1998, see column 4, lines 35-54.	1-38
Y	US 5,914,128 A (LIEBOWITZ et al.) 22 June 1999, see entire document.	1-38

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,916,594 A (LIEBOWITZ et al.) 29 June 1999, see entire document.	1-38
Y	US 6,051,252 A (LIEBOWITZ et al,) 18 April 2000, see entire document.	1-38
Y	US 6,130,326 A (RAMASAMY et al.) 10 October 2000, see entire document.	1-38
Y	US 6,180,639 B1 (COATES et al.) 30 Jqn : 2001, see entire document.	1-38
Y	US 6,335,032 B1 (LIEBOWITZ et al.) 01 January 2002, see entire document.	1-38
Y	RAVIN et al. Preformulation, Chapter 75 in Remington's Pharmaceutical Sciences, 18th Edition. Easton, PA, Mack Publishing Company. 1990, pages 1435-1450, see entire document.	1-38
Y	RUDNIC et al. Oral Solid Dosage Forms, Chapter 89 in Remington's Pharmaceutical Sciences, 18th Edition. Easton, PA, Mack Publishing Company. 1990, pages 1633-1665, see pages 1646 et seq.	1-38
Y	PORTER, Stuart C. Coating of Pharmaceutical Dasage Forms, Chapter 90 in Remington's Pharmaceutical Sciences, 18th Edition. Easton, PA, Mack Publishing Company. 1990, pages 1435-1450, see page 1666 at column 1.	1-38
Y	LONGER et al. Sustained-Release Drug Delivery Systems, Chapter 91 in Remington's Pharmaceutical Sciences, 18th Edition. Easton, PA, Mack Publishing Company. 1990, pages 1676-1693, see entire document.	1-38
Y	O'CONNER et al. Powders, Chapter 88 in Remington's Pharmaceutical Sciences, 18th Edition. Easton, PA, Mack Publishing Company. 1990, pages 1615-1632, see entire document.	1-38